Research and Education Foundation. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. J Am Med Assoc 2007;297:471–9.
[6] Mangano DT, Tudor IC, Dietzel C, Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006;354:353–65.
[7] Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C. Adverse cerebral outcomes after coronary bypass surgery. N Engl J Med 1996;335:1857–63.
[8] D'Agostino Jr RB. Propensity scores in cardiovascular research. Circulation 2007;115:2340–3.
[9] Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.
[10] Fergusson DA, Hébert PC, Mazer CD, Fremes S, Macadams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R, the BART Investigators. A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery. N Engl J Med 2008;358:2319–31.
[11] Ray WA, Stein CM. The Aprotinin Story—is BART the Final Chapter? N Engl J Med 2008;358:2398–400.
[12] Walker AM. Confounding by indication. Epidemiology 1996;7:335–6.
[13] Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, Wijeysundera DN, Fedorko L, Yau TM. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006;46:327–38.
[14] Beattie WS, Karkouti K. Con: aprotinin has a good efficacy and safety profile relative to other alternatives for prevention of bleeding in cardiac surgery. Anesth Analg 2006;103:1360–4.
[15] Furnary AP, Wu Y, Hiratzka LF, Grunkemeier GL, Page 3rd US. Aprotinin does not increase the risk of renal failure in cardiac surgery patients. Circulation 2007;116(11, Suppl.):I127–33.

Editorial comment

Keywords: Aprotinin; Cardiac surgery; Mortality; Late survival

Stamou and colleagues present another critical article about adverse outcome following administration of aprotinin in adult cardiac surgery [1]. In this retrospective study, haemostatic effects of aprotinin were confirmed but the authors found an increased risk for in-hospital cardiac arrest. Another intriguing finding was found, namely that the risk of late cardiac death was higher in patients who received aprotinin than after aminocaproic acid (EACA). Unfortunately, neither the cause of early mortality nor the problem of cardiac-related attrition (graft occlusion, perioperative myocardial infarction, malignant arrhythmias or others) were analysed or specified.

Because of the retrospective character of the study, several limitations and bias have to be considered: the use of aprotinin or EACA was left at the discretion of the surgeons. The patients who received aprotinin were older, had more prior surgery, suffered more frequently from congestive heart failure (NYHA class IV) and underwent more often complex and emergency surgery than those who received EACA. It is questionable if propensity score matching may be sufficient to eliminate 'confounding by treatment' differences of the two study groups. The authors conclude that the risk of aprotinin may not be worth the benefit of reduced transfusion requirements.

There are a tremendous number of publications dealing with aprotinin, but a single finding seems to be consistent: aprotinin is associated with decreased transfusion requirement and re-exploration rate because of bleeding. This was already the main finding of the initial report of Royston and colleagues [2]. In more recent years, the question appeared if aprotinin increases the risk of renal dysfunction and is an independent predictor of increased mortality. Concerning the last two end-points, conflicting results are present in literature.

The two most important 'negative' trials for aprotinin (Mangano et al. [3] as well as the Bart trial [4]) have been largely discussed in literature. Not only the power but also the limitations of these trials are very well pointed out. Some authors believe that the recent 'attacks' against aprotinin may have been statistically unsound [5]. Even extensive meta-analysis of the Cochrane collaboration in 2007 have not found an increased risk of death caused by the use of aprotinin compared to lysine analogues. The use of aprotinin was recommended especially in high-risk patients in whom a substantial blood loss has to be expected [6]. In a more recent update, this option has been contradicted by the same authors [7].

What are the remaining questions? There has been an increasing concern that questions the safety of aprotinin. If we accept this, we are forced to ask why this was not detected during the two decades of extensive use of the drug with published good results. As a result of the aprotinin story [8], studies should — if ever possible — focus on clinical end-points that are not confounded with surrogate markers. Independent clinical safety studies are mandatory even after regulatory approval.

Unfortunately, the large majority of studies that demonstrated adverse outcome following aprotinin were performed using the original Hammersmith protocol, which means a high dosage. More than 15 years ago, we published similar beneficial haemostatic results with low-dose aprotinin and no adverse cardiac outcome was observed, neither early nor late [9]. We do not understand why the low-dose regime was not adopted by more institutions.

Finally, it is today still not clear which patient subgroups may benefit from aprotinin. However, this is more of theoretical interest since the drug is no longer available on a regular basis. Considering that low-risk cardiac surgical patients are at increased risk for bleeding events (e.g., having operation under ongoing combined anti-platelet therapy), other potent measures in addition to the available lysine analogues in order to reduce postoperative bleeding,

the need for transfusion and the incidence of haemorrhagic re-exploration are welcome.

References

[1] Stamou SC, Reames MK, Skipper E, Stiegel RM, Nussbaum M, Geller R, Robicsek F, Lobdell KW. Aprotinin in cardiac surgery patients: is the risk worth the benefit? Eur J Cardio-thorac Surg 2009;36:869—75.
[2] Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 1987;2:1289—91.
[3] Mangano DT, Tudor IC, Dietzel C, Multicenter Study of Perioperative Ischemia Research Group, Ischemia Research, Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006;354:353—65.
[4] Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R, BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319—31.
[5] Grunkemeier GL, Wu Y, Furnary AP. What is the value of a p value? Ann Thorac Surg 2009;87:1337—43.
[6] Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2007. CD001886.
[7] Henry DA, Carless PA, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ 2009;180:183—93.
[8] Ray WA, Stein CM. The aprotinin story—is BART the final chapter? N Engl J Med 2008;358:2398—400.
[9] Carrel T, Bauer E, Laske A, von Segesser LK, Turina M. Low-dose aprotinin also allows reduction of blood loss and blood transfusion after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1991;102:801—2.

Thierry Carrel*, Lars Englberger
Clinic for Cardiovascular Surgery, University Hospital of Berne, Berne, Switzerland
*Corresponding author. Tel.: +41 31 632 23 75; fax: +41 31 632 44 43

E-mail address: thierry.carrel@insel.ch (T. Carrel)

doi:10.1016/j.ejcts.2009.05.015